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REVIEW

Schistosoma excretory/secretory products: an untapped library of tolerogenic immunotherapeutics against food allergy

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Abstract

Food allergy (FA) is considered the 'second wave' of the allergy epidemic in developed countries after asthma and allergic rhinitis with a steadily growing burden of 40%. The absence of early childhood pathogen stimulation embodied by the hygiene hypothesis is one explanation, and in particular, the eradication of parasitic helminths could be at play. Infections with parasites *Schistosoma* spp. have been found to have a negative correlation with allergic diseases. Schistosomes induce regulatory responses to evade immune detection and ensure their long-term survival. This is achieved via excretory/secretory (E/S) products, consisting of proteins, lipids, metabolites, nucleic acids and extracellular vesicles, representing an untapped therapeutic avenue for the treatment of FA without the unpleasant side-effects and risks associated with live infection. Schistosome-derived immunotherapeutic development is in its infancy and novel discoveries are heavily technology dependent; thus, it is essential to better understand how newly identified molecules interact with host immune systems to ensure safety and successful translation. This review will outline the identified *Schistosoma*-derived E/S products at all life cycle stages and discuss known mechanisms of action and their ability to suppress FA.

Keywords: B regulatory cells, extracellular vesicle cargo, immune modulators, proteins and peptides, *Schistosoma*-derived drug discovery, T regulatory cells

INTRODUCTION

The current global prevalence estimate of allergic diseases, including food allergy (FA), is up to 40% of adults and children.[1,2] The environmental exposome, which includes viral and microbial toxins, is well described by the hygiene hypothesis as an important component of immune

education. In addition, gastrointestinal parasites are thought to be pivotal for the development of immune tolerance caused by their powerful ability to evade host immune detection.[3] A compelling number of clinical and epidemiological studies suggest an inverse correlation among parasitic infection, skin prick test (SPT) reactivity and allergy symptom severity.[4–10] It is also important to note the reports of sensitisation and allergic reactions to infection with helminths, such as *Ascaris lumbricoides, Anisakis* and *Schistosoma* spp.[11–13] These are likely a result of the parallel mixed T-helper type 1 (Th1) and 2 (Th2) polarisation and inflammation induced by helminth infections.[14–17] Despite this, a large body of evidence suggests that schistosome infections confer protection against allergic diseases as a result of their capacity to establish more robust tolerance through the induction of both T- and B-regulatory cells.[18–22] These regulatory cells are predominantly activated during chronic schistosomiasis as a result of egg deposition and migration. However, chronic egg production also contributes to significant pathology as a result of aberrant entrapment of eggs in ectopic locations, making the use of therapeutic live infections complex and dangerous.[23] Despite the promising therapeutic indications, extensive unmet need and over a decade of discovery and pre-clinical development on helminth excretory/secretory (E/S) products, too few have progressed to clinical trial. The regulatory responses induced by helminths, including hookworms and schistosomes, offer unique therapeutic opportunities for restoring natural tolerance (regulatory T cells) unlike any other drug or biologics commercially available. Therefore, this review will outline and discuss identified *Schistosoma*-derived E/S products at all life-cycle stages, their known mechanisms and their potential to suppress FA.

WORM-DERIVED BIOLOGIC DISCOVERY RELIES HEAVILY ON TECHNOLOGICAL CAPABILITIES

There are many hurdles that limit the therapeutic breakthrough of helminth-derived molecules. Advances in mass spectrometry-based techniques have allowed for a significant increase in the identification of novel secreted proteins over the past 20 years. However, there is still a gap in access to databases that curate protein sequences and functional information of helminth products. Consultation of conventional databases is not straightforward. This is in part a result of the striking ability of parasites to modify the amino acid sequence (~5–30%) of known orthologous proteins, altering their function and manipulating host immunity to their advantage.[24–27] To effectively characterise molecular composition and function of helminth E/S products, it is essential to isolate and purify large enough concentrations from large-molecular (lipo) protein contaminants, and host, bacterial and parasite residues.[28] The presence of distinct extracellular particles (EPs), such as exomeres, supermeres and extracellular vesicles (EVs), complicates isolation further, necessitating the use of additional steps and modification of standard protocols, resulting in the loss of large proportions of target molecules in the process.[29] Larger volumes of starting material can compensate for this loss; however, the major challenge with helminths is the limited access to the parasite material required for the production of sufficient EPs, which is particular issue with *Schistosoma* spp. caused by their complex life cycle that requires access to mammalian and intermediate snail hosts.[29] As such, obtaining relevant schistosome life cycle stages for culture is limited by infective larvae (cercariae) and the number of parasites that can be collected from sacrificed mammalian hosts.

Finally, a large body of evidence suggests that helminth EVs diverge significantly from their mammalian counterparts, posing a number of unique challenges with consistent isolation and purification of therapeutic EVs for *in vitro* and *in vivo* studies.[30–32] This necessitated the development of additional guidelines to complement the Minimal Information for Studies of EVs (MISEV). Another significant challenge associated with helminth EVs is the generation of sufficient quantities of particles for structural or functional studies, identifying helminth-specific EV markers and successful characterisation. The major reason for further investigation of schistosome-derived compounds as therapeutics for allergic disease, and FA in particular, is their complex life cycle, which includes three distinct life stages within the human host. Each of these stages must undergo a complex migratory process through the lungs, liver, gastrointestinal tract (GIT) and blood vessels, where they are met with a complex host immune response. However, this particular parasite has fine-tuned the release of various mucosal- and cell-specific compounds that show promising applications for dampening

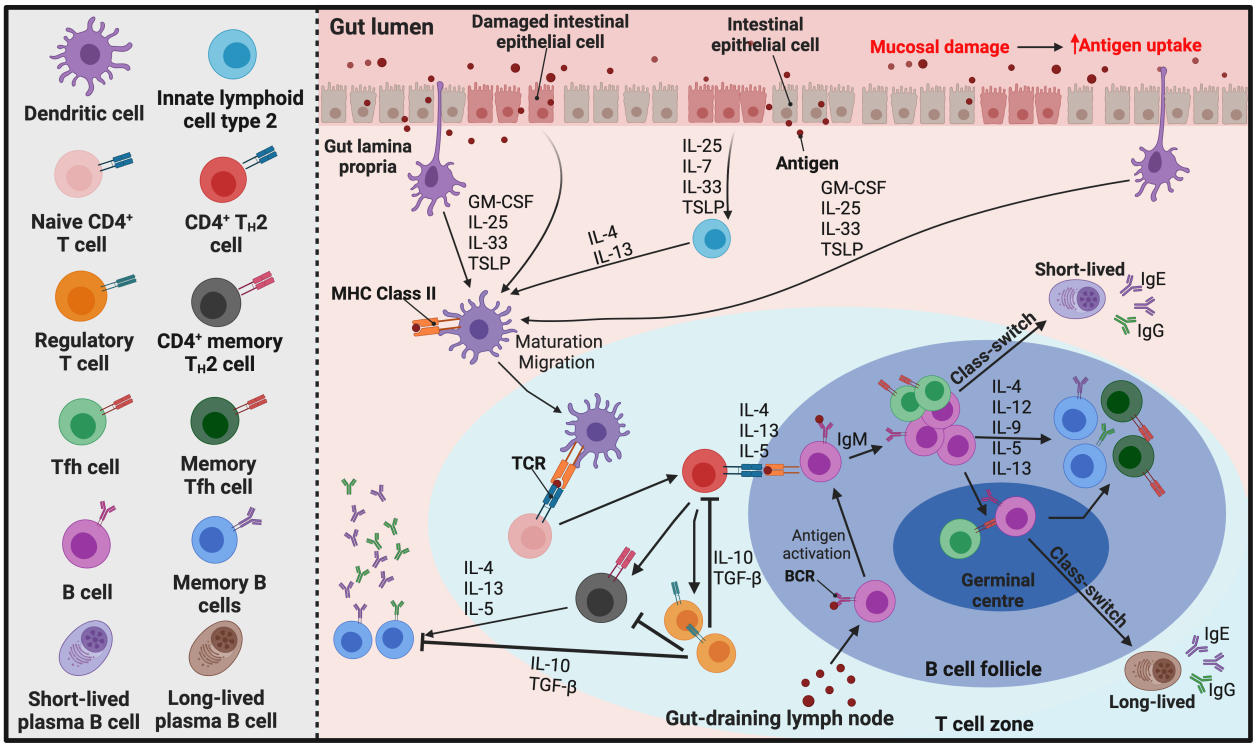

Figure 1. Pathogenesis of allergic sensitisation to food-derived allergens. Damaged intestinal epithelial cells release inflammatory mediators causing type 2 innate lymphoid cell activation and Th2 skewing cytokine production.[124–128] APCs (DCs, B cells and epithelial cells) collect antigens through the gut wall for presentation via MHC class II to naive $CD4^+$ T cells in secondary lymphoid tissue, promoting $CD4^+$ Th2-cell priming. Activated Th2 cells prime B cells in an antigen-specific manner (IgE/IgG), which assist in germinal centre formation or become short-lived plasma cells.[129,130] Tfh cells modulate B-cell selection (high affinity), their differentiation into low- and high-affinity long-lived plasma cells and the build-up of memory effector cells, providing the trigger for allergic response in case of re-exposure.[131,132] APC, antigen-presenting cell; BCR, B-cell receptor; FcR, Fc receptors; GM-CSF, granulocyte–macrophage colony-stimulating factor; Ig, immunoglobulin; IL, interleukin; MHC II, major histocompatibility complex II; TCR, T-cell receptor; Tfh, T follicular helper cell; TGF-β, transforming growth factor beta; Th, T-helper cell; TSLP, Thymic stromal lymphopoietin.

allergen-induced inflammation, suppressing tissue remodelling and restoring allergen tolerance. Therefore, this review will discuss the therapeutic benefits of *Schistosoma* spp. and recent discoveries in schistosome derivatives, such as proteins, EVs and micro-RNAs (miRNA) at all life cycle stages for the treatment of FA.

THERAPEUTIC MANAGEMENT OF FA

The symptoms and severity of FA evolve over time as a result of the complexity and multifactorial nature of the immune response which is typically divided into three phases: sensitisation, immediate hypersensitivity reactions and delayed hypersensitivity reactions. Allergen sensitisation and the subsequent responses to food antigens can be mediated by either immunoglobulin (Ig) E-dependent or -independent mechanisms, or a combination of both (Figure 1).[33] Sensitisation occurs through the progressive development of tissue-resident memory T and B cells, which respond in a dose-dependent manner to allergens and stimulate allergen-specific antibody production.[33] This is an essential process for allergic sensitisation, providing the trigger for allergic response in case of re-exposure, which can result in both immediate reactions, including anaphylaxis and delayed (cell-mediated) allergic reactions (Figure 2).[34–37]

The greatest unmet need in FA is the absence of disease-modifying treatments. The recommendation for symptom management relies on strict allergen avoidance. Antihistamines and leukotriene receptor antagonists, oral steroids and few biologics (anti-IgE or IL-5 antibodies) aim at controlling the downstream inflammatory cascade triggered by

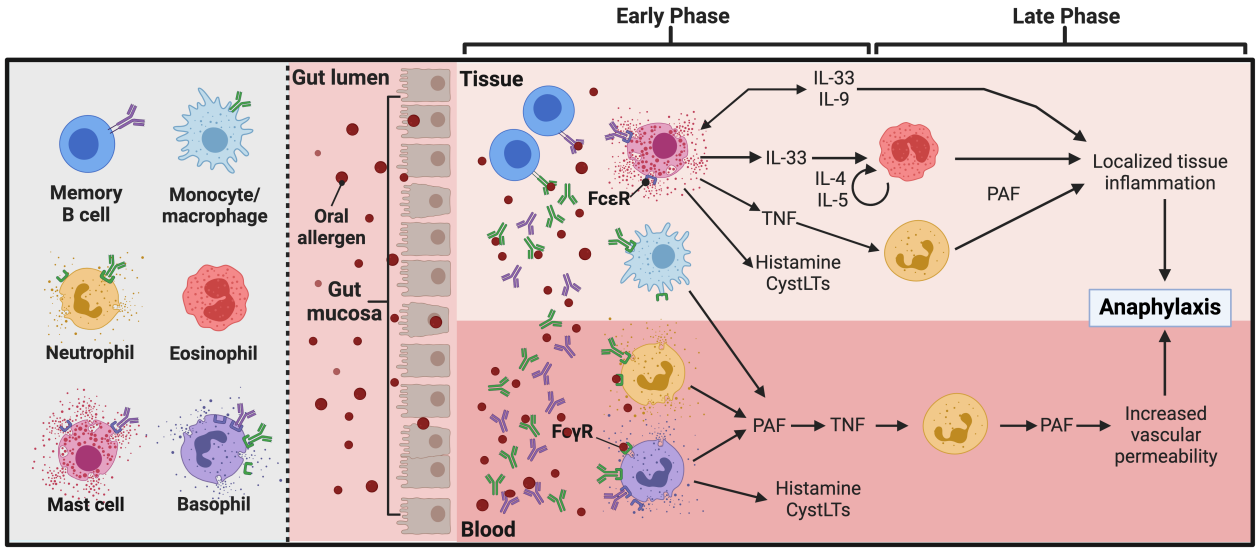

Figure 2. Pathogenesis of allergic challenge reactions to food-derived allergens. Secondary challenge causes allergen-specific antibodies to crosslink to Ig FcεRs (IgE binding) or FcγRs (IgG binding) on granulocytes and phagocytes. This contributes to early- and late-phase reactions. The overwhelming production of inflammatory mediators from granulocytes promotes increased vascular permeability, localised tissue inflammation and, in severe cases, anaphylaxis. cystLT, cysteinyl leukotrienes; FcγRs, Fc gamma receptor; FcεR, Fc epsilon Fc receptor; Ig, immunoglobulin; IL, interleukin; PAF, platelet-activating factor; TNF, tissue necrosis factor.

allergen exposure (Figure 1).[38] Currently, long-term relief is obtained after allergen immunotherapy (AIT), a process aiming to increase the threshold amount of allergen tolerated without promoting the activation of effector responses, especially anaphylaxis (Figure 2).[39] AIT promotes the induction of allergen-specific regulatory T (Tregs) cells, specifically FoxP3^{+} IL-10-producing inducible (i) Tregs. However, IL-10-producing regulatory B cells (Br1) have recently emerged as potential targets for AIT owing to their ability to induce both iTregs and FoxP3^{+} natural (n) Tregs, inhibit dendritic cell (DC) maturation, suppress effector responses and increase serum IgG4.[40] Unfortunately, the therapeutic benefits of AIT are slow to emerge and only temporary, as the entire desensitisation process needs to be repeated every few years. This illustrates the need for novel therapeutic strategies that promote sustained natural tolerance suited for the complex and evolving nature of FA symptoms.

IMMUNE EVASION BY SCHISTOSOMES

A hallmark of schistosomiasis is the induction of Th2 responses, which occur following egg deposition, with IL-4, IL-5, IL-13, eosinophilia and IgE production by B cells. The primary role of this mechanism is to protect the host and reduce worm and egg burden by killing parasites within infected tissues and promoting intestinal expulsion.[41] Most of these modulatory effects are mediated by the release of a suite of modulatory E/S products that ensure the successful establishment of the parasite within the host (Figures 3–5). To infect mammalian hosts, aquatic cercariae penetrate the skin and epithelium, shedding their tail as quickly as a few minutes post-penetration to become schistosomula. After traversing the basal lamina (up to 3 days post-infection), schistosomula enter the dermis and penetrate local capillaries (Figure 3). Schistosomula then migrate to the lung vasculature, where they mature into a more elongated shape to facilitate passage to the portal vein of the liver (Figure 4). Juvenile worms pair up and once mature will migrate to the mesenteric vessels to begin sexual reproduction, releasing between 100 and 300 (*S. haematobium* and *S. mansoni*) and over 2000 (*S. japonicum*) eggs per day (Figure 5).[42] Because of the risk of adverse events during infection, including hypersensitivity reactions induced by skin penetration (cercarial dermatitis), pulmonary migration and initial egg laying (Katayama syndrome) and fibrosis of the liver and surrounding organs caused by aberrantly entrapped eggs (hepatosplenomegaly), live therapy is unlikely to occur.[43] However, countless

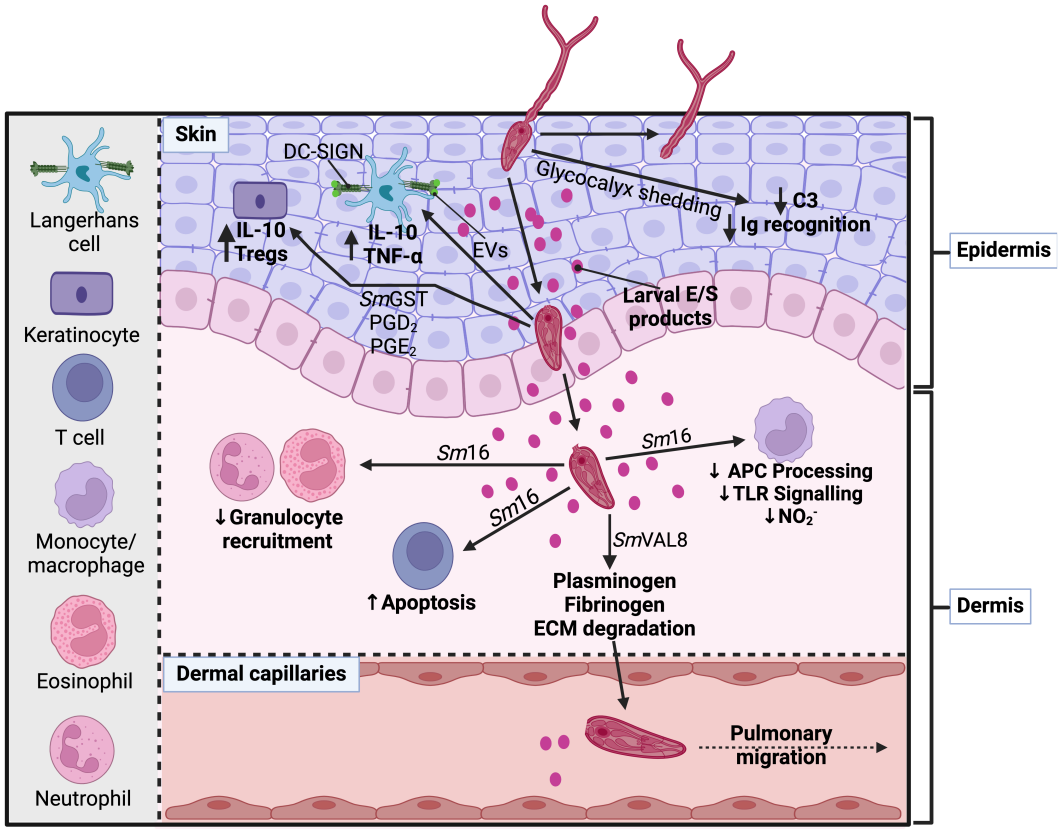

Figure 3. Immune regulation and evasion strategies of *Schistosoma* spp. larval stages in the human host. Cercariae penetrate host **skin** and produce a myriad of proteases to degrade host structural molecules and allow the larvae to penetrate local venules for pulmonary migration. Schistosomula also releases regulatory molecules such as *Sm*16, SmVal8 and prostaglandin to influence immune cell function to promote larvae survival. APC, antigen-presenting cell; C3, complement component 3; DC, dendritic cell; E/S, excretory/secretory products; ECM, extracellular matrix; EVs, extracellular vesicles; Ig, immunoglobulin; IL, interleukin; NO_2, nitrogen dioxide; PGD2, prostaglandin D2; PGE2, prostaglandin E2; *Sm*16, *S. mansoni* 16 kDa immunomodulatory protein; *Sm*GST, *S. mansoni* glutathione S-transferase isoenzyme; *Sm*VAL8, *S. mansoni* venom allergen-like protein 8; TLR, toll-like receptor.

E/S products are produced through this process, including proteins, carbohydrates, lipids, peptides, metabolites, nucleic acids and EPs, capable of altering the host immune function and tissues themselves. This plethora of immunomodulatory compounds produced by schistosomes can be harnessed to benefit FA.

PROTEINS

Larval schistosomes

Schistosomula engage with several different skin-resident innate immune cells during the initial infection stage, including HLA-DR$^+$ (MHC class II receptor) DCs, most likely Langerhans cells and keratinocytes (Figure 3).[44] Larvae rapidly shed their glycocalyx, impeding complement attacks and immunoglobulin recognition by eosinophils and neutrophils.[45] The mechanisms involved in larval migration through the vasculature and the lungs are poorly understood; however, *in vitro* studies suggest that larval survival is heavily reliant on the tight regulation of host CD4$^+$ Th-cell responses (Th2, Th1, Th17 and Treg), favoring Th1/Th17 skewing to ensure larval migration, maturation and survival.[46,47] Larvae and adult worms generate an additional layer of protection from the host during migration by cloaking themselves in blood group antigens, MHC proteins and IgG Fc receptors (FcR) as well as releasing E/S products, such as elastase-like serine proteases that cleaves IgE, to avoid immunoglobulin-based attacks (Figure 4).[48] Few

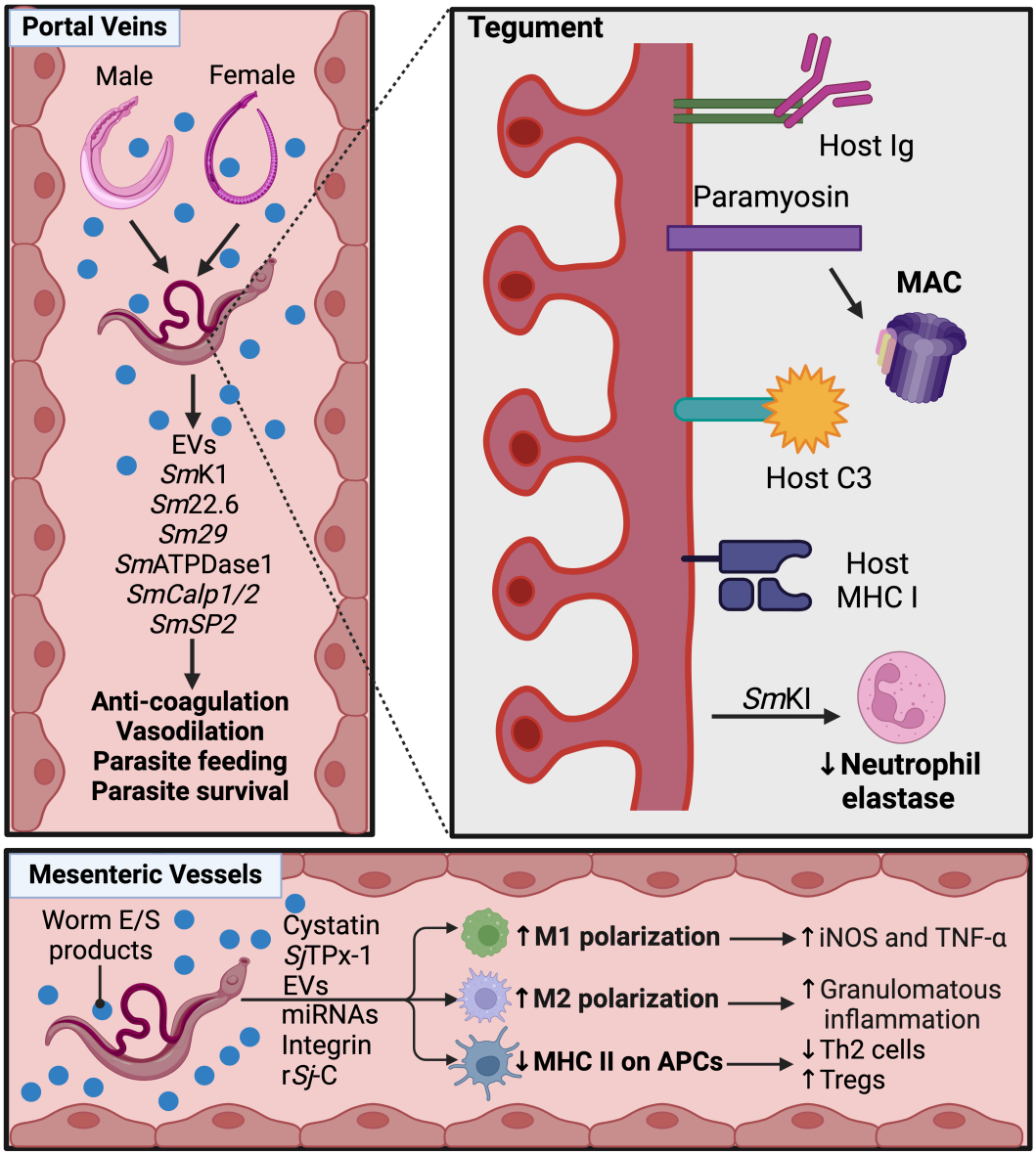

Figure 4. Immune regulation and evasion strategies of *Schistosoma* spp. adult worms in the human host. Following pulmonary migration, elongated immature worms migrate to the **portal veins**, where they pair up and finish maturing. During this time, the worms release a myriad of compounds in their E/S products that impede coagulation and promote vasodilation and parasite feeding/survival. Adult worms also incorporate host factors into their tegument and release modulatory compounds to evade host immune response. Coupled adults then move to the **mesenteric vessels** of the host intestines and worms their E/S molecules to ensure the survival of their eggs prior to extravasation and during migration. C3, complement component 3; E/S, excretory/secretory products; EVs, extracellular vesicles; Ig, immunoglobulin; MAC, membrane attack complex; MHC I, major histocompatibility complex class I; *rSj*-C, recombinant *S. japonicum* cysteine protease inhibitor; r*Sj*-C, recombinant *S. japonicum* cysteine protease; *Sj*TPx-1, *S. japonicum* thioredoxin peroxidase-1; *Sm*22.6, 22 kDa adult *S. mansoni* antigen; *Sm*29, 29 kDa adult *S. mansoni* antigen; *Sm*ATPDase1, *S. mansoni* ATP diphosphohydrolase; *Sm*Calp1/2, *S. mansoni* calpain protease 1/2; *Sm*KI, *S. mansoni* serine protease inhibitor; *Sm*SP2, *S. mansoni* serine protease 2.

of these proteins have been further characterised *in vivo*/*in vitro*; however, *S. japonicum* thioredoxin peroxidase (r*Sj*TPx) was shown to reduce CD86 and MHC class II expression on macrophages, which downregulates antigen presentation and effector T-cell activation.[49] *Sm*16, a 16.8 kDa

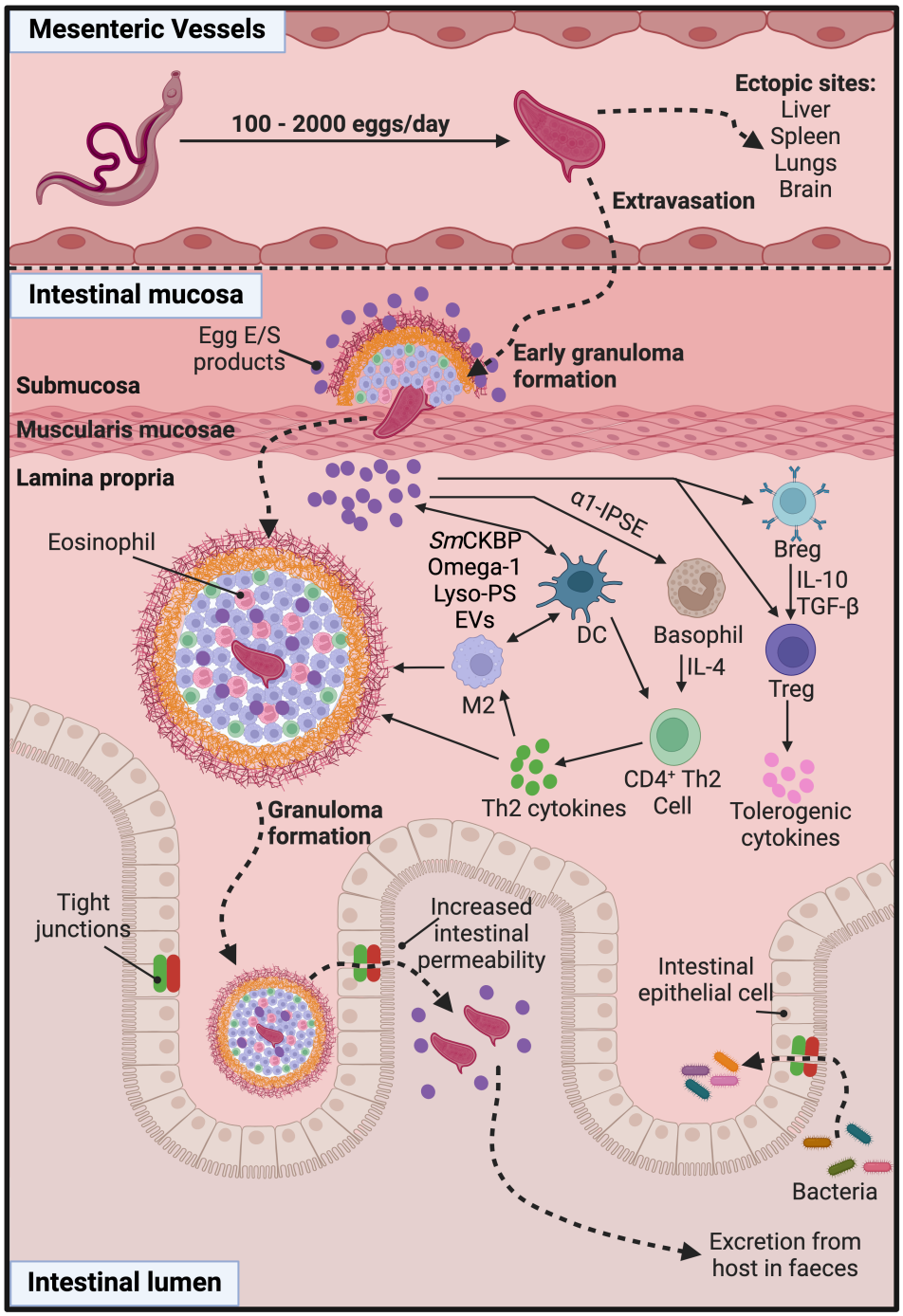

Figure 5. Immune regulation and evasion strategies of *Schistosoma* spp. eggs in the human host. Following oviposition, eggs must extravasate out of the mesenteric vessels and migrate through the intestinal mucosa into the lumen for excretion in faeces. To facilitate this, schistosome eggs manipulate the host granulomatous immune response by producing E/S compounds, which promote Th2 granulomatous inflammation, M2 polarisation and decrease leukocyte recruitment. In addition, migrating eggs E/S products promote regulatory T-cell (Treg) expansion both directly and indirectly through the activation of regulatory B cells (Breg). This complex interaction between migrating eggs and the host immune cells allows for safe passage of eggs through the intestinal mucosa without causing lasting damage to the host tissue. 20:1 Lyso-PS, schistosomal lysophosphatidylserine; E/S, excretory/secretory products; IL, interleukin; M2, macrophage type 2; omega-1, *S. mansoni* glycoprotein; *Sm*CKBP, *S. mansoni* chemokine-binding protein; TGF-β, transforming growth factor beta; Th, T-helper cell; α1/IPSE, alpha 1/IL-4-inducing principle of *S. mansoni* eggs.

S. mansoni larval and egg protein, assists in early survival by compromising classical macrophage activation, dermal neutrophil migration and eosinophil recruitment to slow antigen presentation and delay the effector T-cell response (Table 1).[50] *Sm*16 is the major protein involved in promoting IL-1ra to suppress effector T-cell activation in the skin, giving it potential as a therapeutic for inflammatory skin disorders.[51] Recombinant r*Sj*16, the *S. japonicum* homologue of *Sm*16, has been shown to induce alternative macrophage activation, splenic $CD4^+FoxP3^+$ Tregs, suppression of DC activation and $CD4^+CD25^-$ T cells and increased IL-10 and IFN-γ production *in vitro* and *in vivo*.[52,53]

Few experimental studies have been performed exploring the benefit of larval infection in allergy. *S. japonicum* lung stage infection was shown to ameliorate ovalbumin (OVA)-induced allergic airway inflammation (AAI) in mice.[54] The migrating larvae induced the proliferation of $CD4^+CD25^+Fox3^+$ Treg in the lungs and draining lymph nodes via the upregulation of Epor and Klra17 and the downregulation of B-cell activation genes Dock2, Irf4, Rac2, Lgals3, H2-Oa, Pdcd1lg2, Sash3 and Mzb1, resulting in a significant decrease in OVA-specific IgE levels. Despite their primary localisation to the skin and lungs, schistosomula are in direct contact with the host microcirculation, making it likely that larval E/S products could promote a tolerogenic immune environment in the GIT in preparation for egg laying and migration. Therefore, all larval stages of *Schistosoma* spp. infection offer a range of tolerogenic E/S products and represent an untapped library of compounds that could reduce allergic inflammation.

Adult schistosomes

Adult schistosomes home to the mesenteric veins of the small bowel (*S. mansoni, S. japonicum*) or vesicle venules of the bladder (*S. haematobium*) and begin oviposition (5–8 weeks post-infection). During this time, Th1 cytokine (TNF-α, IL-3 and IFN-γ) levels decrease, and the immune response becomes more Th2 skewed (6–8 weeks post-infection) to destroy migrating eggs and reduce parasite burden. This Th2 bias is achieved by promoting IL-4, IL-5 and IL-13 production, Ig class switching to IgE on B cells and eosinophil expansion.[55] As with schistosomula, adult worms secrete E/S products to avoid detection (Figure 4). Many of these products originate from the tegument, the dynamic outer surface of the schistosome that rapidly sheds and self-renews.[56] *S. japonicum* tetraspanning orphan receptor (*Sj*TOR) is a tegument-derived product aimed at fighting complement-mediated parasite death.[57] Schistosomes secrete their E/S products to regulate and minimise Th2-induced pathology within the host caused by egg laying and migration, with the percentage of Tregs ($CD4^+CD25^+FoxP3^+$) in granulomas peaking between 8 and 12 weeks after infection.[58] In mice, *Sj*-C (*S. japonicum* tegument-derived cysteine protease) reduced antigen presentation in splenic DCs via MHC class II complexes, leading to the proliferation of $CD4^+CD25^+Foxp3^+$ Tregs and the production of IL-4, TGF-β and IFN-γ (Figure 4).[59] IL-10 also plays a central role, with 1-(11Z-eicosenoyl)-glycero-3-phosphoserine 20:1 (20:1 lyso-PS) actively inducing IL-10-producing Tregs through TLR2/6 heterodimer activation on DCs.[60,61] Interestingly, an important role was identified for the IL-4 receptor alpha (IL-4Rα) signalling to potentiate the suppressive functions of Treg *in vivo*, illustrating the importance of the multifactorial aspect of the host–parasite cross-talk during infection.[62] Adult worms therefore appear to produce a suite of immunomodulatory compounds that induce type 2 immunity, which could be beneficial to promote gut repair and mucosal healing, and tolerogenic processes responsible for the induction and activation of $CD4^+CD25^+FoxP3^+$ Tregs and the careful modulation of IL-4/IL-10 production.

The therapeutic properties of adult worm E/S products have been investigated either using direct injection of soluble worm antigen (SWA) (whole or derivatives) or indirectly via single-sex infection models. In the latter, mice and humans are infected with only male cercariae to avoid egg production, ensuring that the host is only exposed to adult worm-derived products.[63] *Schistosoma* spp. live infections have been shown experimentally to protect against allergy, inflammatory bowel disease, arthritis and anaphylaxis.[64] In 2020, a controlled human trial ($n = 17$) using *S. mansoni* male-only infections was undertaken, where all volunteers exhibited schistosome worm and egg-specific IgG1, antigen-specific $CD4^+$ T-cell production of Th2 and IFN-γ cytokines.[63] However, despite the lack of egg production, 18% of volunteers experienced

Table 1. Classification of *Schistosoma* species-derived proteins involved in promoting tolerogenic pathways

Moiety	Life stage	Species	Compound	Target	Result	Reference
Protein	Cercariae/ Schistosomulae	*S. mansoni*	Larval extracts and culture supernatants	Hu IgE	Proteolytic cleavage via $C_{\epsilon}2/C_{\epsilon}3$ domain interface of heavy chain	20
		S. japonicum	r*Sj*TPx	Ms Macrophage	↓MHC II; ↓CD86 expression on macrophages	21
		S. mansoni	r*Sm*16	Ms Macrophage (BMD)	Delayed antigen presentation; ↑IL-10 and ↓IL-23p40; TLR independent; TLR2 independent may limit cercarial dermatitis	90
		S. japonicum	r*Sj*16	Ms Dendritic cells (BMD)	↓DC Maturation; ↑IL-10; ↓IL-12p70, IL-6 and IL-2; ↓T $CD4^+$-cell activation; IL-10 dependent	25
		S. japonicum	r*Sj*16	Ms $CD4^+$ T cells	↑$CD4^+CD25^+Foxp3^+IFN\text{-}\gamma^+T\text{-}bet^+$ Tregs; ↓$CD4^+CD25^-$ T cells; ↑IL-10 and IFN-γ production	24
		S. japonicum	Lung stage infection	Ms Lung cells (whole)	Partial AAI protection; ↓IgE; ↑Lung $Foxp3^+$ Tregs, ↑Lung B-cell genes	26
		S. mansoni	*sm*LEV1	Ms Liver cells (PBMCs)	↓Hepatic granulomas	83
	Adult worm	*S. mansoni*	Male worm infection	Ms IL-10^+ Bregs	Protection from anaphylaxis; ↑IL-10^+ Bregs, ↑IL-10 and ↓IL-4; $CD4^+$ T-cell independent	42
		S. mansoni	Male worm infection	Ms Tregs	Partial AAI protection; ↑Lung IL-10 and IL-4; ↓EPO and IL-5	38
		S. mansoni	*sm*29 SWA (PIII)	Ms Lung Bregs; BAL	Full AAI protection; ↑lung $Foxp3^+$ Tregs; ↓BAL IL-4 and IL-5 (PIII only)	39
		S. mansoni	*sm*22.6	Ms Lung cells (whole), BAL	Full AAI protection; ↑lung $Foxp3^+IL\text{-}10^+$ Tregs and IL-10; ↓IgE; ↓BAL EPO, IL-4 and IL-5	
		S. mansoni	*sm*200 *sm*KI-1	Ms Lung cells (whole)	Full AAI protection; ↓lung IL-4 and IL-5; ↓serum IgE; ↓lung EPO (*sm*KI-1 only)	
		S. mansoni	*Sm*teg	Ms Lung $CD11b^+F4/80^+IL\text{-}10^+$ DCs; $CD11c^+CD11b^+IL\text{-}10^+$ macrophages; BAL	Reduced AAI pathology; ↑ IL-10; ↓lung IL-13 and IL-5; ↓BAL IgE and eosinophils	91
		S. mansoni	20:1 Lyso-PS	HEK-TLR2 cells	TLR2 activation	33
		S. japonicum	r*Sj*-C	Ms Dendritic cells	Inhibits antigen presentation of exogenous antigens; ↑Splenic $Foxp3^+$ Tregs	31
		S. japonicum	SJMHE1 (peptide)	Ms Tregs, Th1 $CD4^+$ T cells	Full AAI protection; ↑Lung and spleen $Foxp3^+$ Tregs; ↑IL-10, IL-35 and IFN-γ; ↓IL-4 and TGF-β	40
	Eggs	*S. mansoni*	r*Sm*16	Hu macrophages (THP-1)	↓IL-6, IL-1β, GM-CSF, I-309, TNF-α and IL-10; ↑PPAR and LXR/RXR to regulate macrophage metabolism	22
		S. mansoni	Freeze-killed eggs	Ms $Foxp3^+IL\text{-}10^-$ Tregs	Full AAI protection; ↑lung $Foxp3^+IL\text{-}10^-$ Tregs; ↑lung IL-10; ↓BAL IL-5, IL-4, IL-13, CCL2, CCL3 and CCL5; ↓serum IgE	67
		S. mansoni	SEA	IMR-90 fibroblasts	Protection from inflammation (time dependent); ↓LPS-induced JAK/STAT1 signalling, ↓phosphorylated STAT1 (dose-dependent); ↓IL-6, IL-8, IL-1β and IFN-γ	71
		S. mansoni	Freeze-killed eggs SEA IPSE	Ms IL-10^+ Bregs; $Foxp3^+$ Tregs	↑Splenic IL-10^+ Bregs; ↑$FoxP3^+$ Tregs; ↑IL-10; ↑$CD1d^+$ IL-10^+ human B cells; IPSE is an IgE-binding factor secreted from subshell area of eggs	72
		S. mansoni	rHis-IPSE	Hu basophils	↑Histamine, IL-13, IL-4 and agglutination	92

(Continued)

Table 1. Continued.

Moiety	Life stage	Species	Compound	Target	Result	Reference
		S. mansoni	$CD19^+CD1d^+IL\text{-}10^+$ splenic B cells from infected mice (adoptive transfer)	Ms $Foxp3^+$ $IL\text{-}10^+$ Tregs	Full AAI protection; ↑$FoxP3^+IL\text{-}10^+$ Tregs in lungs, BAL and MedLNs; ↑IL-10	73
		S. mansoni	Live infection (egg producing)	Ms $IL\text{-}10^+$ Bregs	Full AAI protection; ↓ IL-5, IL-13 and eosinophils in BAL; ↓IL-4, IL-5, IL-13 and IL-10 in MedLNs	74
		S. mansoni	$CD19^+IL\text{-}10^+$ pulmonary B cells from infected mice (adoptive transfer)	Ms lung cells (whole), Ms $Foxp3^+$ $IL\text{-}10^+$ Tregs	**Lung:** partial AAI protection; ↓BAL eosinophils; IL-10 independent **Spleen:** full AAI protection, IL-10 dependent; increased ↑IL-10; ↑lung and BAL $CD4^+CD25^+FoxP3^+IL\text{-}10^+$ Tregs	
		S. mansoni	Live infection (egg producing)	Ms Tregs	Full AAI protection; ↓AAI (eosinophils); ↑lung and medLN $CD4^+CD25^+FoxP3^+$ Tregs	69
		S. mansoni	T-cell epitopes on *Sj*p40 protein (P6, P25, P30)	Ms IFN-g^+CD4^+ T cells	Reduced AAI pathology; ↑splenic $CD4^+IFN\text{-}\gamma^+$ T cells and IFN-γ; ↓splenic $CD4^+IL\text{-}4^+$ T cells; ↓splenic IL-4, IL-5, IL-13; ↓serum IgE and IgG1/IgG2a ratio	70
		S. mansoni	Live infection (egg producing)	Ms lung Bregs	Full AAI protection; ↑Lung CD86 expression; ↓Th2 cytokine production; $CD25^+FoxP3^+$ Treg independent; Partially IL-10/TGF-β independent	60
		S. japonicum	SEA	Transwell system with SEA-treated RAW264.7 cells and HSCs	↑Liver fibrosis; SEA-treated macrophages produce miR-33-containing EVs; EV uptake activates HSCs by ↑SOCS3; ↑TGF-β	93
		S. japonicum	Live infection (egg-producing)	Ms Tregs	Full AAI protection; ↑Splenic $CD4^+CD25^+Foxp3^+$ Tregs; ↓IgE; ↓lung and BAL eosinophils, neutrophils, IL-5, IL-4, IL-17 and IFN-γ	94
		S. japonicum	Splenic $CD4^+CD25^+Foxp3^+$ Tregs (adoptive transfer) from infected mice	Ms $CD4^+CD25^+$ Tregs (spleen)	Reduced AAI pathology; ↑splenic $CD4^+CD25^+$ Tregs; ↑serum TGF-β; ↓BAL eosinophils; ↓$CD4^+CD25^+TGF\text{-}\beta^+$ IL-10 dependent	65

20:1 Lyso-PS, 1-(11Z-eicosenoyl)-glycero-3-phosphoserine 20:1; AAI, allergic airway inflammation; BMD, bone marrow-derived; CCL, chemokine ligand; FoxP3, forkhead box P3; HSC, hepatic stellate cell; HSC, hepatic stellate cells; Hu, human; i.p., intraperitoneal; i.v., intravenous; IL, interleukin; ILN, inguinal lymph node; iNOS, inducible nitric oxide synthase; IPSE, IL-4-inducing factor from *S. mansoni* eggs; LXR/RXR, liver X receptor/retinoid R receptor; MAP3K7, mitogen-activated protein kinase kinase kinase 7; MenLN, mediastinal lymph nodes; MLN, mesenteric lymph node; moDC, monocyte-derived dendritic cells; Ms, mouse; Mφ, liver macrophage; OVA, ovalbumin; PPAR, peroxisome proliferator-activated receptor; rHis-IPSE, recombinant His-tagged IPSE; rSj16, *S. japonicum* 16 kDa protein; r*Sj*-C, *S. japonicum* tegument-derived cysteine protease; r*Sj*TPx, recombinant thioredoxin peroxidase of *S. japonicum*; s.c., subcutaneous; SEA, soluble egg antigen; *Sj*, *Schistosoma japonicum*; SLN, sentinel lymph node; *Sm*, *Schistosoma mansoni*; *Sm*16, *S. mansoni* 16 kDa protein; *Sm*KI, *S. mansoni* serine protease inhibitor; SWA, soluble worm antigen; TGF-β, tissue growth factor-beta; TNF-a, tumor necrosis factor alpha.[34]

severe adverse side effects, including cercarial dermatitis and acute schistosomiasis, illustrating the continuing risks associated with therapeutic use of live schistosome infections. Few adult worm-derived immunomodulatory molecules have been identified and tested in allergic diseases. Most studies use models of AAI (Table 1) and show a significant modulation of Th2 responses in favor of IL-10 production in the lung.[65,66] Male-only worm (*S. mansoni* and *S. japonicum*) infections and an *S. japonicum* worm-derived peptide (SJMHE1) can suppress AAI to both house dust mite (*Dermatophagoides pteronyssinus*) and OVA/alum models by decreasing eosinophilia and increasing lung Tregs ($CD4^+CD25^+FoxP3^+IL\text{-}10^+$).[67,68] These studies also observed a reduction in IL-4- and IL-5-producing Th2 cells, IFN-γ-producing Th1 cells and IL-17-producing Th17 cells, and reduced allergen-specific IgE following adult worm antigen exposure. Recently, recombinant *Sm*200 and *Sm*KI-1 proteins were found to suppress *Blomia. tropicalis*-induced AAI in mice by altering IL-10 production in the lung and decreasing IL-4, IL-5 and eosinophil peroxidase (EPO) production. In addition, *Sm200* enhanced IL-10 production in PBMCs from atopic individuals, although the target cell nor the source of the cytokine was further identified (Table 1).[69]

Finally, *S. mansoni* single-sex infection was shown to fully ameliorate anaphylaxis to penicillin V in mice.[70] Protection was mediated by both IL-10-producing Bregs and $FoxP3^+$ Tregs, which were induced either directly via antigen presentation or expanded as a result of the pro-tolerogenic environment created by IL-10-producing Bregs. Given the similarities between food- and drug-induced allergies, these results provide significant insight into the immune mechanism by which adult schistosomes may protect from FA. It is important to note that studies in *S. mansoni* on male versus female worms during infections have indicated marked differences in their transcriptional profile and immune function, with female worms often overlooked despite their essential role in promoting tolerance during infections.[71,72] As such, single-sex infections are an imperfect way to study the effects of worm-only infection in allergic disease, making crude worm E/S and purified derivatives from both sexes essential to accurately study worm-only effects and the development of potential FA therapeutics.

Schistosome eggs

Following oviposition, schistosome eggs extravasate through the endothelium and migrate through the gut mucosa to exit the host and renew their life cycle (Figure 5).[73] Extravasated eggs immediately become the target of Th2 granulomatous inflammation. These modified granulomas are highly organised multicellular structures consisting of an egg surrounded by M2 macrophages (recruited from $Ly6C^{hi}$ monocytes), IL-4-, IL-5- and IL-13-producing Th2 $CD4^+$ cells, eosinophils and mast cells, all of which are encapsulated by stromal cells/fibroblasts.[74] The function of granulomas is to entrap and destroy migrating eggs while protecting the host from cytotoxic egg secretions. However, in an act of immune trickery, *Schistosoma* spp. eggs have co-evolved to manipulate host Th2 granulomas and promote their own migration through the gut mucosa into the gut lumen (Figure 5).[75] Within the granulomas, mature eggs release their E/S compounds, which contain a myriad of immunomodulatory molecules that have unique 'adhesive' characteristics (proteins, glycoproteins and carbohydrates) which is used to create a pro-regulatory environment close to the egg to promote a 'safe pathway' for the granulomas (with the egg safe inside) to follow into the gut lumen.[76–78] *Schistosoma* spp. E/S products are predominantly taken up by myeloid and plasmacytoid DCs (mDCs and pDCs, respectively), as well as B cells resulting in phenotypic and functional modifications (Figure 5).[79–81] For example, *S. mansoni* omega-1 (Ω-1), a glycoprotein, is the primary Th2 inducer secreted by eggs due a Ω-1 has a glycosylation pattern that allows uptake by mouse bone marrow-derived DC mannose receptors, causing Th2 polarisation, type 2 cytokine production, M2 macrophage activation and Th2 granuloma-mediated egg migration[82–87] *S. japonicum*-infected mice show a significant expansion of splenic B1 ($CD19^+CD11b^+CD5^{+/-}$) cells that activate follicular and cytotoxic T cells.[88,89] These B cells were shown to upregulate CD5, CD23, PD-L1 and TGF-β and *S. mansoni* chronic egg production promoted Fas ligand-, IL-4- and IL-10-expressing Bregs, enhancing apoptosis of $CD4^+$ and $CD8^+$ effector cells.[20,90–92] The tolerogenic activity of *S. japonicum* egg antigens on splenic B cells was shown to be TLR7 dependent.[88] This suggests that schistosome egg E/S products are potent inducers of tolerance via the differentiation and/or expansion of Bregs. AAI models suggest that schistosome-induced Bregs are distinct from classical

Bregs and are able to impair Th2 activation and promote tolerance independently of Tregs and APCs respectively. The regulatory potential of these schistosome-stimulated Bregs is heavily reliant on IL-10 and TGF-β production.[18]

Eggs are the primary stimulator of Tregs, including both nTregs and iTregs. However, functional studies have only focused on $CD4^+CD25^+FoxP3^+$ phenotypically defined cells to address schistosome-suppressive mechanisms essential for regulating Th1 and Th2 responses.[93] IL-10 production by Tregs in hepatic granulomas has been reported to inhibit Th1/Th2 cytokine production by DCs and iTregs, effectively suppressing egg-killing Th2 responses.[94,95] However, IL-10 production in response to *S. japonicum* egg deposition also provides important negative feedback signals to Tregs, creating a favorable Th2 environment to facilitate granuloma formation and life cycle progression.[96] Exogenous administration of IL-10 to OVA-sensitised animals following the adoptive transfer of $CD4^+CD25^+$ Tregs purified from *S. japonicum*-infected donors protected from AAI.[97] Furthermore, *ex vivo* restimulation of splenocytes from these mice with *S. mansoni* crude egg extract in the presence of recombinant IL-10 resulted in a decreased frequency of TGF-β-expressing Tregs as well as their TGF-β expression levels.[97]

Several studies have demonstrated that crude SEA or whole freeze-killed eggs are a source of immunomodulatory compounds for the treatment of AAI (Table 1).[98–100] Interestingly, epitope mapping of the *S. japonicum* egg-derived protein *Sj*P40 identified several IFN-γ-producing pro-Th1 immunodominant peptides capable of dampening OVA-induced AAI.[101] However, despite the decrease in lung IL-4, IL-5 and IL-13, as well as allergen-specific IgE levels, the degree of protection induced by these products was significantly less robust compared to Breg- and/or Treg-mediated regulation.[102] Recently, crude *S. japonicum* SEA was shown to alleviate OVA-induced AAI by upregulating lung and spleen $CD4^+CD25^+FoxP3^+$ Tregs and decreasing eotaxin, IL-4, IL-1β and IL-18 in BAL. Importantly, using liquid chromatography and *in vitro* Treg induction experiments, this study identified nine target Treg-promoting proteins (Table 1). Finally, *in vitro* stimulation of IMR-90 lung fibroblasts with SEA protected from LPS-induced inflammation by downregulating inflammatory cytokine production (IL-6, IL-8, IL-1β and IFN-γ). This was achieved by modulation of the Janus kinase (JAK)/signal transducer and activator of transcription (STAT)-1 pathway, an essential pathway to allergic disease progression.[103] Few egg-derived proteins have fully resolved mechanisms of action; however, these studies indicate that these compounds have exquisite abilities to regulate the pro-inflammatory molecular pathways at a systemic level that will benefit FA.

The important therapeutic differentiation of schistosomes, and eggs, in particular, is the induction of Bregs. Indeed, the IL-4-inducing principle of *S. mansoni* eggs (IPSE)/alpha-1 can specifically target $CD23^{low}CD21^+$ mouse splenic marginal zone B cells by upregulating CD86 expression and IL-10 production to promote regulatory skewing (Table 1). Co-culture of IPSE/alpha-1-conditioned Bregs with naive $CD4^+CD25^-$ splenic T cells induced $CD25^+FoxP3^+$ Treg polarisation.[104] Adoptive transfer of *S. mansoni*-conditioned $CD1d^+$ Bregs into OVA-sensitised mice suppressed AAI by recruiting $FoxP3^+$ Tregs to the lung in a CD1-dependent manner. This capacity to modulate B cells was also validated in human PBMCs where the regulatory activity of $CD1d^+$, but not $CD24^+CD27^+$ transitional- or IL-10-producing $CD24^+CD38^+$ Bregs, was enhanced following SEA or rIPSE/alpha-1 stimulation.[105] *S. haematobium*-infected Gabonese children were also found to have increased $CD1d^{hi}$ IL-10-producing circulatory Bregs, which significantly reduced following praziquantel (anti-schistosome) treatment.[19,22] These studies highlight the essential role of schistosome-induced Bregs in promoting mucosal trafficking, Tregs and promoting a pro-tolerogenic environment.

EXTRACELLULAR VESICLES

Extracellular vesicles are a diverse family of membrane-bound EPs secreted by all cell types and are classified depending on their intracellular origin, size and cargo.[106] The discovery and characterisation of EV derivatives for therapeutic development is still in its infancy; however, helminths have a demonstrated ability to achieve host–parasite/parasite–parasite communication by producing EVs.[107] As a result of the lack of consistent protein markers, EV populations are often defined by size, including small EVs (sEVs) under 200 nm and medium/large EVs (m/l EVs) over 200 nm. EVs are produced by all helminth life cycle stages and enact immunomodulatory functions on host immune cells through a myriad

of cargo moieties.[108] These include functional and pathogenic proteins, carbohydrates, lipids, metabolites and nucleic acids (microRNA, tRNA mRNA, lncRNA, sncRNA and DNA).[109] Because of their size and high membrane-to-cytoplasm ratio, a large portion of these EV cargo moieties are attached to the vesicles' surface.[110]

Schistosomula-derived extracellular vesicles

Schistosomes release EVs to regulate multiple processes specific to each stage of their life cycle, promoting migration, maturation, immune evasion and survival.[109] There are limited schistosomula-derived EV studies to date and most focus on *in vitro* characterisation and vaccine development (Table 2). Schistosomula-derived EVs can be internalised by human $CD1a^+$ monocyte-derived DCs (moDCs) and Chinese hamster ovarian (CHO) epithelial cells via CD209 (DC-SIGN) as a result of the presence of several fucosylated glycan ligands on their surface.[30] The gut is home to distinct populations of tissue-specific moDCs, including tissue-resident $Ly6C^+CD11b^+CX3CR1^+CD64^-CD14^+MHCII^+$ moDCs (lamina propria) and migratory lysozyme-expressing $CD4^-CD11c^+CD11b^+CX3CR1^+BST2^+MHCII^+$ moDCs (lysoDCs) (Peyer's patches).[111–116] Current understanding of moDCs is their important roles in orchestrating mucosal inflammation during inflammation through antigen presentation, decreased chemokine and cytokine release and promoting Th1/Th2-cell activation at the expense of regulatory responses. In contrast, EV uptake by moDCs via DC-SIGN increased expression of CD80, CD86 and PD-L1, and production of IL-10 and IL-12, suggesting EVs may be capable of altering moDCs to inhibit inflammation and induce Tregs via APC modulation.[31] Finally, vaccination of mice with schistosomula-derived EVs or *Sj/Sm* larval EV protein 1 (LEV1) reduced IFN-γ-mediated Th2 granulomatous inflammation and increased IgG1.[117,118] These results suggest that cercarial/schistosomula EVs and their glycan-rich cargo promote tolerogenic phenotypes in epithelial cells and moDCs and inhibit Th2 immune responses.

Adult worm-derived extracellular vesicles

The therapeutic potential of adult worm-derived EVs in allergic disease is underexplored (Table 2). *S. mansoni* adult EVs are rapidly internalised *in vitro by* naive splenic and human Jurkat T cells, where they release miRNA cargo, including *miR-10*, *bantam* and *miR125*. These miRNAs were also detected in Th cells from gut-associated lymph nodes (mesenteric lymph node and Peyer's patches), suggesting they may play a restricted role in gastrointestinal immune modulation. Mechanistically, *miR-10* restricted Th2 differentiation via mitogen-activated protein kinase kinase kinase 7 (MAP3K7) and decreased NF-κB expression in all cases.[119] Recently, CHO epithelial cells we shown to internalise worm EVs via macrophage galactose-type lectin (MGL/CD301) caused by membrane-bound GalNAcβ1–4GlcNAc (LDN)-containing N-glycans.[30] Finally, *S. mansoni* tetraspanin 2/3 was shown to be essential for internalisation of worm EVs by human endothelial and monocytic cells.[120] Therefore, adult EV-derived miRNA use cell-specific mechanisms to modulate host mucosal, APC and effector T-cell responses and downregulate inflammatory Th2 immune responses, making them of great interest to FA treatment.

Egg-derived extracellular vesicles

Most of the egg-derived EVs characterised thus far have displayed a noticeable affinity for the liver and the spleen; however, their biodistribution within the GIT is yet to be characterised (Table 2). Interestingly, the hepatic cellular uptake of *S. japonicum* EV-derived *miR-71b* and *bantam* (found in adult worm EV) was observed *in vitro* using Hepa1-6 (murine liver) cell line as well as *in vivo* in infected animals.[121] This suggests that schistosome EVs share some homologous miRNA cargo across life stages that exhibit immune cell-specific mechanisms. Further supporting this, a seminal 2020 study further demonstrated the anti-fibrotic function of *S. japonicum miR-71a*, which biodistributed mainly to the liver, thymus and spleen. This miRNA specifically inhibited hepatic stellate cell activity through the downregulation of semaphorin (Sema) 4D expression and the suppression of TGF-β/SMAD and IL-13/STAT6. Additionally, *Sja*-miR-71a increased $CD3e^+CD4^+CD25^+FoxP3^+$ and $CD3e^+CD4^+FoxP3^+T\text{-}bet^+$ Tregs in the spleens and livers of *S. japonicum*-infected mice while decreasing Th1/Th2/Th17 effector responses caused by their expression of Sema4D.[122] *S. japonicum Sja*-miR-71a-containing EVs were shown to be internalised by macrophages and neutrophils,

Table 2. *Schistosoma* species-derived extracellular vesicles and mechanisms involved in immunoregulation

Moiety	Life stage	Species	Compound	Target	Result	Reference
EVs	Cercariae/ Schistosomulae	*S. mansoni*	Culture media EV	Hu moDCs (PBMCs)	Uptake via DC-SIGN/CD209; ↑IL-10 and TNF-α mRNA	82
		S. mansoni	Culture media EV	Hm CHO CLR-expressing cells	Uptake mediated by DC-SIGN/CD209; EVs have highly fucosylated glycan profile	81
	Adult worm	*S. mansoni*	Culture media EV	Hm CHO CLR-expressing cells	Uptake via MGL/CD301; membrane-bound LDN-containing N-glycans	
		S. mansoni	Culture media EV and MV	HUVEC and THP-1 monocytes	EV internalisation dependent on *Sm*-TSP-2/3	86
		S. mansoni	miR-10	Ms $CD4^+$ T cells	↓Th2-cell polarisation via MAP3K7	85
		S. japonicum	Culture media EV	RAW264.7 macrophages	↑CD16/CD32 (M1); ↑iNOS and TNF-α	95
		S. japonicum	miR-125b bantam	RAW264.7 macrophages	↑M1 and M2 activation	96
	Eggs	*S. japonicum*	Culture media EVs and Sja-miR-71a	Ms hepatic stellate cells (HSC)	↓Fibrosis pathways (HSC activation); ↓Sema4D, ↓TGF-β1 (TGF-β1/SMAD) and ↓IL-13 (IL-13/STAT6); ↓a-SMA and collagen-1; biodistributed to lungs, liver and thymus	88
				Infected Ms $CD3e^+CD4^+$ T cells	↑Spleen and liver $CD3e^+CD4^+CD25^+FoxP3^+$ and $CD3e^+CD4^+FoxP3^+T\text{-}bet^+$ Tregs	
		S. japonicum	Culture media EVs and Sja-miR-71a	Ms BMD macrophages and neutrophils; Ms liver cells (whole)	PPAR-γ agonist; ↓Semaphorin 4D; ↑IL-10; ↓Mets and NETs	89
		S. mansoni	Culture media purification	IgG	↑Serum IFN-γ and IgG; ↓adult worms; ↓intestinal eggs; ↓granuloma volume	84

a-SMA, alpha smooth muscle actin; BMD, bone marrow derived; CHO, Chinese hamster ovary epithelial cells; CLR, C-type lectin receptor; EV, extracellular vesicle; HUVEC, human umbilical vein endothelial cells; LDN, GalNAcβ1–4GlcNAc; M1/M2, type 1/2 macrophage; MET, macrophage extracellular traps; MGL/CD301, macrophage galactose-type lectin; miR, microRNA; MV, microvesicle; NETs, neutrophil extracellular traps; PPAR-γ, peroxisome proliferator-activated receptor gamma; *Sj*, *Schistosoma japonicum*; *Sm*, *Schistosoma mansoni*; SMAD, suppressor of mothers against decapentaplegic; STAT, signal transducer and activator of transcription; TSP, tetraspanin.

acting as a peroxisome proliferator-activated receptor (PPAR)-γ agonist to decrease Sema4D and increase IL-10 production, inhibiting the formation of macrophage and neutrophil extracellular traps.[123] Whether schistosome egg-derived EVs and their miRNA cargo enact similar regulatory processes in the GIT is yet to be elucidated; however, the above data illustrate the essential role of egg-derived EVs in promoting tolerance and controlling inflammatory Th1/Th2/Th17 activation to promote survival. Given the essential role of gastrointestinal egg migration for survival, it is likely that egg EVs also enact similar tolerogenic mechanisms in the GIT, making them relevant to FA.

CONCLUSIONS

Although schistosome infections and their E/S products appear to confer protection against allergic diseases, the risks associated with the live parasite make their therapeutic exploitation complicated and costly. The different mucosal immune environments in the vasculature versus the GIT make it essential to characterise schistosome-mediated tolerance in the gut, requiring a deeper understanding of localised regulatory immune reactions to migrating eggs. However, when considering the vast number of soluble compounds excreted/secreted by parasites throughout their life stages as described in this review, schistosomes certainly present an untapped source of highly potent immunomodulatory molecules. There is a considerable list of compounds already identified that, based on their proposed mechanism of action, are worth evaluating in models of allergic diseases. Schistosomes appear to have a strong immunomodulatory effect on B cells, and the capacity to induce Bregs as well as Tregs, which are essential for restoring natural tolerance to FA.

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AUTHOR CONTRIBUTIONS

Madeleine Rogers: Visualization; writing – original draft; writing – review and editing. **Sandip Kamath:** Supervision; writing – review and editing. **Donald McManus:** Project conception; writing – review and editing. **Malcolm Jones:** Supervision; writing – review and editing. **Catherine Gordon:** Supervision; validation; writing – review and editing. **Severine Navarro:** Project administration; supervision; validation; writing – review and editing.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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